

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

see form PCT/ISA/220

X 16357

PCT

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY
(PCT Rule 43bis.1)

11 Jun 2005

Date of mailing
(day/month/year) see form PCT/ISA/210 (second sheet)

Applicant's or agent's file reference
see form PCT/ISA/220

FOR FURTHER ACTION
See paragraph 2 below

International application No.
PCT/US2004/022299

International filing date (day/month/year)
30.07.2004

Priority date (day/month/year)
11.08.2003

International Patent Classification (IPC) or both national classification and IPC
C07D223/16, A61K31/55, A61P25/22, A61P25/24, A61P25/30, A61P3/04

Applicant
ELI LILLY AND COMPANY

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☒ Box No. II Priority
- ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☒ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

2. FURTHER ACTION

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA"). However, this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1b/s(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of three months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA:



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WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.
 - ☐ This opinion has been established on the basis of a translation from the original language into the following language , which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).
2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:
 - a. type of material:
 - ☐ a sequence listing
 - ☐ table(s) related to the sequence listing
 - b. format of material:
 - ☐ in written format
 - ☐ in computer readable form
 - c. time of filing/furnishing:
 - ☐ contained in the international application as filed.
 - ☐ filed together with the international application in computer readable form.
 - ☐ furnished subsequently to this Authority for the purposes of search.
3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.
4. Additional comments:

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No.
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Box No. II Priority

1. ☒ The following document has not been furnished:
- ☒ copy of the earlier application whose priority has been claimed (Rule 43*bis*.1 and 66.7(a)).
 - ☐ translation of the earlier application whose priority has been claimed (Rule 43*bis*.1 and 66.7(b)).
- Consequently it has not been possible to consider the validity of the priority claim. This opinion has nevertheless been established on the assumption that the relevant date is the claimed priority date.
2. ☐ This opinion has been established as if no priority had been claimed due to the fact that the priority claim has been found invalid (Rules 43*bis*.1 and 64.1). Thus for the purposes of this opinion, the international filing date indicated above is considered to be the relevant date.
3. Additional observations, if necessary:

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No.
PCT/US2004/022299

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

- ☐ the entire international application,
- ☒ claims Nos. 3-12

because:

- ☒ the said international application, or the said claims Nos. 3-12 for industrial applicability relate to the following subject matter which does not require an international preliminary examination (*specify*):

see separate sheet

- ☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):
- ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.
- ☐ no international search report has been established for the whole application or for said claims Nos.
- ☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:
 - the written form ☐ has not been furnished
 - ☐ does not comply with the standard
 - the computer readable form ☐ has not been furnished
 - ☐ does not comply with the standard
- ☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.
- ☐ See separate sheet for further details

**WRITTEN OPINION OF THE
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International application No.
PCT/US2004/022299

Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes: Claims	1-32
	No: Claims	
Inventive step (IS)	Yes: Claims	
	No: Claims	1-32
Industrial applicability (IA)	Yes: Claims	1,2,13-32
	No: Claims	

2. Citations and explanations

see separate sheet

Box No. VI Certain documents cited

1. Certain published documents (Rules 43*bis*.1 and 70.10)

and /or

2. Non-written disclosures (Rules 43*bis*.1 and 70.9)

see form 210

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING
AUTHORITY (SEPARATE SHEET)**

International application No.

PCT/US2004/022299

~~AP20 Rec'd PCT/PRO~~ 09 FEB 2006

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

Claims 3-12 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(I) PCT).

Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

Reference is made to the following documents:

- D1: WO 02/074746 A1 (YAMANOUCHI PHARMACEUTICAL CO.) 26 Sept 2002
- D2: US-A-4 100 278 (NEDELEC LUCIEN ET AL) 11 July 1978
- D3: WO 93/00094 A (SMITHKLINE BEECHAM PLC) 7 January 1993
- D4: WO 03/045940 A (FU JIAN-MIN ; UPJOHN CO (US)) 5 June 2003
- D5: GB-A-1 225 053 (GEIGY AG) 17 March 1971

1.

With regard to the prior art disclosed in the documents cited above the subject-matter of the present application, i.e 7-chloro-6-(trifluoroethylamino)-2,3,4,5-tetrahydro-1H-benzo[d]azepine as 5-HT_{2c} receptor agonist, appears to fulfil the requirements of novelty, cf. Article 33(2) PCT:

D5 is related to 6-chloro-2,3,4,5-tetrahydro-1H-benzo[d]azepine that has an anorexigenic action.

D4 discloses 2,3,4,5-tetrahydro-1H-benzo[d]azepine compounds as 5-HT receptor agonists, which are always substituted on the nitrogen atom the azepine ring.

The 2,3,4,5-tetrahydro-1H-benzo[d]azepine compounds of D3 and D1, used as 5-HT receptor agonists, differ from those claimed on account of a different substitution pattern on the benzene ring.

The 5-HT receptor inhibitors of D2 have a 2,3,4,5-tetrahydro-1H-benzo[b]azepine structure.

2.

The present application is related to 7-chloro-6-(trifluoroethylamino)-2,3,4,5-tetrahydro-1H-benzo[d]azepine as 5-HT_{2c} receptor agonist and therefore useful in the treatment of depression, anxiety or obesity.

D3 is considered to be the closest prior art document since it discloses 2,3,4,5-tetrahydro-1H-benzo[d]azepine compounds, used as 5-HT receptor agonists, but which differ from the claimed compounds on account of a different substitution pattern on the benzene ring. D1 discloses also 2,3,4,5-tetrahydro-1H-benzo[d]azepine compounds as 5-HT receptor agonists, wherein the substituents are specifically attached in position 6 and 7 of the 2,3,4,5-tetrahydro-1H-benzo[d]azepine ring.

Starting from the generic disclosure of D3, wherein R¹ can be So_nR⁴R⁵ with R⁴ as haloalkyl and R⁵ as-H and using the teaching of D1, wherein the substituents are fixed in positions 6 and 7 of the 2,3,4,5-tetrahydro-1H-benzo[d]azepine ring, the skilled person, faced with the problem of providing further 5-HT_{2c} receptor agonists, would have been unambiguously led to prepare the compounds of the present application.

Hence, the underlying technical problem to be solved by the present invention has to be seen in the provision of 5-HT_{2c} receptor agonists, which present an unexpected effect with regard to the compounds of D1/D3. Nevertheless, the description does not contain an evidence or further information for surprising effect with regard to D1/D3.

At the present stage and in the absence of evidence for such surprising effect compared to D1/D3, no inventive step can be acknowledged and Article 33(3) PCT cannot be considered to be satisfied.

3.

For the assessment of the present claims 3-12 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

Re item VI
certain documents cited

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING
AUTHORITY (SEPARATE SHEET)**

International application No.

PCT/US2004/022299

Application No Patent No	Publication date (day/month/year)	Filing date (day/month/year)	Priority date (valid claim) (day/month/year)
WO03086306	23.10.2003	11.04.2003	12.04.2002
WO03099792	04.12.2003	28.05.2003	29.05.2002

These documents are also related to 2,3,4,5-tetrahydro-1H-benzo[d]azepine compounds used as 5-HT receptor agonists.